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Handgrip strength improves prediction of type 2 diabetes: A prospective cohort study

Running Head: Handgrip strength predicts diabetes

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ABSTRACT

Purpose: We aimed to determine whether handgrip strength (HGS) improves type 2 diabetes (T2D) risk prediction beyond conventional risk factors.

Design: Handgrip strength was assessed at baseline in 776 individuals aged 60-72 years without a history of T2D in a prospective cohort. Handgrip strength was normalised to account for the effect of body weight. Hazard ratios (HRs) (95% confidence intervals [CI]) and measures of risk discrimination for T2D and reclassification [net reclassification improvement (NRI), integrated discrimination index (IDI)] were assessed. **Results:** During 18.1 years median follow-up, 59 T2D events were recorded. The HR (95% CI) for T2D adjusted for conventional risk factors was 0.49 (0.31-0.80) per 1 standard deviation higher normalized HGS and was 0.54 (0.31-0.95) and 0.53 (0.29-0.97) on adjustment for risk factors in the DESIR and KORA S4/F4 prediction models, respectively. Adding normalized HGS to these risk scores was associated with improved risk prediction as measured by differences in -2 log likelihood, NRI and IDI. Sex-specific HRs and risk prediction findings using sensitive measures suggested the overall results were driven by those in women. **Conclusion:** Adding measurements of HGS to conventional risk factors might improve T2D risk assessment, especially in women. Further evaluation is needed in larger studies.

Keywords handgrip strength; type 2 diabetes; risk prediction; cohort study

KEY MESSAGES

- Handgrip strength (HGS) is independently associated with reduced risk of type 2 diabetes (T2D), but its utility in classifying or predicting T2D risk has not been explored.
- In this prospective cohort study of older Caucasian men and women, adding measurements of HGS to conventional risk factors improved T2D risk assessment, especially in women.
- Assessment of HGS is simple and inexpensive and could prove a valuable clinical tool in the early identification of people at high risk of future T2D.

Introduction

Though several established risk factors such as older age, obesity, family history of type 2 diabetes (T2D), physical inactivity, smoking, and excessive alcohol consumption explain a large proportion of the risk of T2D, identification of individuals at increased risk of T2D remains a difficult undertaking. Some of these conventional risk factors are sometimes not present in individuals identified to have developed T2D. Hence, there is a need for further identification of easily measurable factors that could have predictive relevance for T2D. Handgrip strength (HGS), used as a measure of muscular strength, has emerged as a strong risk indicator for adverse vascular outcomes as well as mortality.(1, 2) Until recently, there was diverging evidence on the link between HGS and the risk of T2D. Based on a pooled analysis of 10 prospective cohort studies,(3) we have demonstrated that increased HGS is independently associated with reduced risk of T2D. Although the independent association of HGS with risk of T2D is suggestive of its usefulness in risk prediction, such information is insufficient for making judgements in clinical practice about its potential utility in classifying or predicting T2D risk in individuals.(4) Various measures which have been proposed for evaluating the predictive accuracy of a risk marker include risk discrimination and reclassification.(5) Given that the assessment of HGS is inexpensive and quick to do and with the absence of any evidence about its potential value in T2D risk prediction strategies, its potential utility for T2D risk assessment warrants detailed investigation. Using a population-based sample of participants free from T2D at baseline, we report the extent to which HGS measurements could improve the prediction of T2D in a general population setting using measures of risk discrimination and reclassification.

Materials and methods

Study design and population

We conducted this study in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Supplementary Material 1**). We used primary data from the Kuopio Ischemic Heart Disease (KIHD) study, a population-based prospective cohort study which was designed in Kuopio, Finland, to investigate emerging risk factors for vascular disease and other related chronic diseases.(6) Details of the study design and recruitment have been reported previously.(1) In the initial KIHD study, participants comprised a representative sample of men recruited from the city of Kuopio and its surrounding rural communities in eastern Finland. Re-examinations were conducted for these participants underwent at 4 years, 11 years and 20 years after study entry. Women were invited to join the original study during the 11-year examinations, and this was the cohort that was employed for the current analysis. A total of 2,358 participants (1007 men and 1351 women) aged 53 to 74 years were initially recruited for this cohort.(7) Of the 2,072 participants found to be potentially eligible, 193 did not agree to participate, 66 did not respond to the invitation and 39 declined to provide informed consent, which left 1,774 participants who had baseline examinations conducted from March 1998 to December 2001.(7) A subset of 875 randomly selected eligible participants had HGS measurements at the 11-year re-examination (baseline examination for this cohort). Of the 1,774 participants, we excluded 143 participants with a pre-existing history of diabetes. This was followed by further exclusion of 840 participants who did not have data on HGS measurements and 15 participants with missing covariate data. The current analysis is based on 776 men and women without a history of T2D at baseline and with complete information on HGS, relevant covariates, and T2D cases (**Supplementary Material 2**). The institutional review board of the University

of Kuopio and Kuopio University Hospital, Kuopio, Finland (License number 143/97) approved the study research protocol. Written informed consent was obtained from all participants and all study procedures were conducted according to the Declaration of Helsinki.

Assessment of HGS and relevant risk markers

The dominant hand of each study participant was used in the measurement of HGS using a hand dynamometer (in kPa; Martin-Balloon-Vigorimeter; Gebrüder Martin, Tuttlingen, Germany). Two measurements were taken, and their mean value was used for analysis; there was a one-minute resting gap between both measurements. The dynamometers were calibrated at the beginning of each test. To account for the influence of body weight and to normalize the data, absolute values of HGS were allometrically scaled (normalized HGS = HGS/body weight$^{2/3}$).(8, 9) All results were multiplied by 100 for easier readability.(9) Study procedures including blood sample collection, measurement of blood-based markers, physical measurements, and assessment of lifestyle characteristics have been described previously.(7, 10) Self-reported questionnaires were used to assess baseline socio-demographic and lifestyle characteristics, existing medical conditions and use of medications.(11) The energy expenditure of physical activity was assessed from a validated 12-month leisure-time physical activity questionnaire.(12)

Ascertainment of incident T2D

All incident T2D cases that occurred from study entry to 2018 were included. An incident T2D case was defined as a fasting plasma glucose (FPG) ≥ 7.0 mmol/l, a 2 h glucose tolerance test plasma glucose ≥ 11.1 mmol/l, or use of glucose-lowering medication according to self-report at re-examination and by record linkage to the national hospital discharge registry and to the Social Insurance Institution of Finland register for reimbursement of medicine expenses.

Statistical analyses

Descriptive analyses were used to summarise baseline characteristics of participants; means (standard deviation, SD) or medians (interquartile range, IQR) for continuous variables and percentages for categorical variables. To examine the association of baseline levels of HGS with risk of T2D, hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard models after confirming no substantial departure from the assumptions of proportionality of hazards.(13) Normalized HGS was modeled per SD increase. Adjustment for covariates were based on four models: (Model 1) age and sex; (Model 2) model 1 plus high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), smoking status, physical activity, family history of diabetes, and FPG; (Model 3) including component variables in the the 9 year Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) risk score (i.e. smoking, parental history of diabetes, hypertension, and waist circumference) (14) employed for the risk prediction analyses; and (Model 4) including risk factors in the Cooperative Health Research in the Region of Augsburg (KORA) S4/F4 model (i.e. age, sex, BMI, smoking, parental diabetes, hypertension and glucose) which was developed to specifically predict the risk of T2D in older subjects (15, 16). As we accounted for the influence of body weight during computation of our exposure (normalized HGS), BMI was replaced with waist circumference to avoid overfitting of the model. The selection of covariates in model 2 was based on their established role as risk factors for T2D, evidence from previous research,(3, 17, 18) or their potential as confounders based on known associations with T2D and observed associations with the exposure using the available data. Given the few events in the study (n=59), only a few covariates were chosen at a time in each model to avoid overfitting. We evaluated if the overall association between HGS and T2D was modified by sex using tests of interaction and this was conducted for models 1, 2 and 4 because of similar adjustment for

confounders in both genders.

To assess whether adding information on HGS to conventional T2D risk factors is associated with improvement in prediction of T2D risk, we employed distinct statistical approaches. First the improvement in risk discrimination resulting from adding HGS information to a model containing the DESIR variables(14) was quantified using Harrell's C-index.(19) The C-index is appropriate for time-to-event data and provides the probability that the model correctly predicts the order of failure of randomly selected pairs of individuals. A C-index of 1.0 indicates perfect prediction of the order of failure (in this case T2D), whereas a C-index of 0.5 is achieved purely by chance. We employed the individual variables included in the risk score rather than published formulas in the original study because these are based on different populations and time points and outcomes may be slightly different. Furthermore, using individual variables rather than published scores is conservative because models with individual variables usually predict outcomes better than the scores, and it is more difficult for new variables to improve risk prediction.(20) The 95% CIs for C-indices and their changes were derived from jackknife standard error. Comparison of the C-index for models including and not including information on HGS was performed according to the methodology of DeLong(21) and with the Stata command "somersd". Second, we calculated the continuous net reclassification improvement (NRI) (22), a category-free version of the NRI (which does not depend on the arbitrary choice of categories and determines whether risk increases to any extent for cases under a new model compared to the old or reference model, and similarly whether risk decreases to any degree for non-cases). Finally, we calculated the integrated discrimination improvement (IDI), which integrates the NRI over all possible cut-offs and mathematically corresponds to the difference in discrimination slopes of the 2 models in comparison.(5)

Given that Harrell's C-index is based on ranks rather than on continuous data, it can be insensitive in

detecting differences.(23, 24) To avoid discarding potential biomarkers that can be used in risk prediction, sensitive risk discrimination methods such as the -2 log likelihood test have been recommended.(23, 24) Therefore, in addition to Harrel's C-index which has disadvantages such as being based on ranks only, not being able to assess calibration and findings may not be of clinical importance,(25) we tested differences in the -2 log likelihood of prediction models with and without inclusion of HGS. Sex-specific analyses were also conducted. Given that the KORA S4/F4 model(15, 16) seemed to perform better in the KIHD cohort, we also explored model improvement on addition of information on HGS.

Exploration of the data suggested a missing completely at random mechanism, hence we did not anticipate a complete-case analysis would have produced biased estimates. However, given that about 50% of the original participants did not have data on HGS measurements, we conducted multiple imputation by chained equations (MICE) to handle potential selection bias originating from missingness. The imputation model included all model covariates as well as T2D outcome status. Given the computational time required, 10 imputations were computed. Cox regression analyses were run across the 10 imputed datasets and the pooled estimates were reported. All statistical analyses were conducted using Stata version MP 16 (Stata Corp, College Station, Texas).

Results

Handgrip strength and risk of T2D

The overall mean (SD) age of study participants at study entry was 69 (3) years and 47.2% were males. The mean (SD) values of normalized HGS and weight were 0.49 (0.23) kPa/kg$^{2/3}$ and 75.2 (12.9) kg respectively (**Table 1**). Except for baseline levels of HGS, weight, BMI, waist circumference and FPG, there were no significant differences in clinically relevant subgroups and levels of risk markers between

participants who did and did not develop T2D. Individuals who developed T2D had lower HGS and higher levels of weight, BMI, waist circumference and FPG. Baseline characteristics by sex are presented in **Supplementary Material 3**.

During a median (interquartile range, IQR) follow-up of 18.1 (12.1-19.2) years, a total of 59 T2D cases (annual rate 4.92/1,000 person-years at risk; 95% CI: 3.81-6.35) were recorded. The age- and sex-adjusted HR for T2D per 1 SD increase in normalized HGS was 0.38 (95% CI: 0.24-0.57) which was minimally attenuated to 0.49 (95% CI: 0.31-0.80) on further adjustment for established risk factors and other potential confounders (HDL-C, SBP, smoking status, physical activity, family history of diabetes, and FPG) (**Table 2**). In a third model that adjusted for risk factors in the DESIR risk score, there was still evidence of an association 0.54 (95% CI: 0.31-0.95), which was minimally attenuated to 0.51 (95% CI: 0.28-0.94) on additional adjustment for FPG. In the fourth model which adjusted for risk factors in the KORA S4/F4 score, the HR for T2D per 1 SD increase in normalized HGS was 0.53 (95% CI: 0.29-0.97).

In sex-specific analyses, normalized HGS was strongly and inversely associated with T2D in women, whereas there was no evidence of an association in men (**Table 2**). Data was imputed for 1,631 participants and the imputed results were broadly similar to those obtained using observed values (**Supplementary Material 4**).

Handgrip strength and T2D risk prediction

Results of risk prediction analyses are presented in **Table 3**. A T2D risk prediction model (DESIR) containing established risk factors yielded a C-index of 0.6596 (95% CI: 0.5904, 0.7288). After addition of information on normalized HGS, the C-index was 0.6979 (95% CI: 0.6261, 0.7698), representing a

marginal significant increase of 0.0383 (-0.0047, 0.0814; *p*=0.08). On investigating differences in the -2 log likelihood of the DESIR score, the -2 log likelihood was significantly improved on addition of normalized HGS to the DESIR score (*p* for comparison=0.01). The continuous NRI and IDI were 23.33% (95% CI -27.17, 73.83; *p*=0.37) and 0.0062 (95% CI -0.0007, 0.0132; *p*=0.08) respectively. On addition of normalized HGS to the KORA S4/F4 score, the C-index change was (0.0182; *p*=0.17), difference in -2 log likelihood (*p*=0.01), NRI (58.44%; *p*=<.001) and IDI (0.0062; *p*<.001). The results were stronger in women compared to men (**Tables 3-4**).

Discussion

Our findings of an inverse and independent association between baseline normalized HGS and T2D risk generally concur with previous population-based cohort studies as well as our recent pooled analysis of 10 studies on the topic.(3) Our sex-specific analyses suggested evidence of effect modification; there was a strong inverse association in women, whereas there was no evidence of an association in men. Given the low number of events in men and women, these findings need to be interpreted with caution. Indeed, in our meta-analysis of existing studies, we found no evidence of effect modification by sex.(3) With regards to the potential utility of HGS measurements for T2D risk assessment, the addition of information on normalized HGS to two different risk models containing traditional risk factors for T2D was associated with an improvement in the discrimination of T2D risk using measures such as NRI, IDI and difference in -2 log likelihood, a more sensitive measure when evaluating the added predictive value of a new measurement. The findings were more remarkable in women and appeared to drive these overall results.

The mechanistic pathways underlying the association between increased HGS and reduced T2D risk have been extensively discussed in our pooled analysis of 10 studies evaluating the association between HGS and T2D.(3) Briefly, factors proposed to mediate this effect include reduction in higher muscle mass, incidence of weight gain, abdominal adiposity, insulin resistance, and inflammation;(26) decrease in visceral fat deposition and improvement in insulin sensitivity and glycaemic control;(27) as well as frailty.(28) Apart from the low number of events, the differences in the results for men and women may partly be explained by marked differences in body composition (eg, lean mass, muscle strength, percent body fat).

The current findings of a strong independent association between HGS and T2D risk and the added prognostic value of HGS on top of established risk factors may have several implications for the development of T2D prevention strategies. Assessment of HGS is simple, inexpensive and does not require very skilled expertise and facilities/resources. Handgrip strength is assessed quantitatively using a dynamometer and this involves the subject squeezing its handles with maximum isometric effort and maintaining this for 5 seconds. The use of HGS in risk assessment can easily be adopted in any clinical setting, whether general or specialized. However, given the low number of events in our analyses and some of the marginally significant findings, we propose larger studies to replicate these findings and robustly assess if information on HGS might aid in the early identification of people at high risk of future T2D. Furthermore, there is a need to identify further preventive strategies for T2D. Though it is quite well established that physical activity can prevent or delay T2D,(29, 30) resistance training should be promoted as a population-wide approach for the prevention of T2D, given its effectiveness in increasing muscle mass and strength, thus reducing visceral fat deposition and improving insulin sensitivity and glycaemic control.(27)

Several strengths of this evaluation deserve mention and they include the novelty, being the first study to assess the potential utility of HGS measurements in T2D risk prediction; use of a well-characterised cohort of men and women who were nationally representative; employment of the MartinVigorimeter in assessment of HGS, given its high reliability and accuracy when assessing grip strength in older patients;(31) the use of allometric scaling to normalize HGS data; the long and complete follow-up of study participants; the use of sensitive measures such as the -2 log likelihood in our formal risk prediction analyses; the use of a category-free NRI, which has the advantage of not requiring pre-specified categories and does not lose information due to categorization;(25) and finally the use of multiple imputation methods, which showed that the results of our complete-case analyses were not biased. Limitations of the current study which were mostly inherent included: (i) inability to generalize the findings to other age groups and ethnicities; (ii) the inability to correct for regression dilution because of absence of repeat measurements of HGS, hence the observed associations could be underestimated; (iii) the low number of incident cases of T2D, which precluded detailed sex-specific analyses and establishment of cut-offs for men and women; and (iv) the potential for residual confounding due to other unknown or unmeasured covariates such as frailty and andropause.

Conclusion

In a predominantly older Caucasian population, we have confirmed previous findings of an inverse and independent association between HGS and T2D risk, which appears to be modified by sex. These new data suggest adding measurements of HGS on top of conventional risk factors improves T2D risk prediction, especially in women when using sensitive measures like the -2 log likelihood test. Given the

low number of events in the current KIHD cohort, further evaluation is needed in studies with larger samples, other age groups and populations.

Disclosure of interest

The authors report no conflicts of interest.

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TABLE 1 Baseline participant characteristics, overall and by incident T2D status

	Overall (N=776) Mean (SD), median (IQR) or n (%)	**Developed T2D (N=59) Mean (SD), median (IQR) or n (%)**	**No T2D (N=717) Mean (SD), median (IQR) or n (%)**	***p*-value**
Normalized handgrip strength (kPa/kg$^{2/3}$)	0.49 (0.23)	0.39 (0.13)	0.49 (0.24)	.001
Questionnaire/Prevalent conditions				
Age at survey (years)	69 (3)	69 (3)	69 (3)	.86
Males	366 (47.2)	24 (40.7)	342 (47.7)	.30
Family history of diabetes	258 (33.3)	21 (35.6)	237 (33.1)	.69
Current smokers	74 (9.5)	6 (10.2)	68 (9.5)	.98
History of hypertension	347 (44.7)	27 (45.8)	320 (44.6)	.87
Physical measurements				
Weight (kg)	75.2 (12.9)	81.9 (12.5)	74.7 (12.8)	<.001
Height (cm)	164 (9)	163 (8)	164 (9)	.38
BMI (kg/m^2)	27.9 (4.3)	30.8 (5.1)	27.6 (4.2)	<.001
Waist circumference (cm)	92.4 (11.7)	98.3 (11.3)	92.0 (11.6)	<.001
SBP (mmHg)	139 (18)	140 (21)	138 (17)	.52
DBP (mmHg)	80 (9)	82 (11)	80 (9)	.12
Energy expenditure of total LTPA (kcal/day)	386 (232-680)	407 (258-702)	382 (231-677)	.93
Blood-based markers				
Total cholesterol (mmol/l)	5.48 (0.93)	5.31 (0.91)	5.50 (0.93)	.14
HDL-C (mmol/l)	1.25 (0.31)	1.19 (0.27)	1.25 (0.31)	.11
FPG (mmol/l)	4.90 (0.52)	5.45 (0.58)	4.86 (0.48)	<.001

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LTPA, leisure-time physical activity; SD, standard deviation; SBP, systolic blood pressure; T2D, type 2 diabetes

TABLE 2 Overall and sex-specific association of normalized handgrip strength with type 2 diabetes

	Overall (776 participants, 59 cases)		**Men (366 participants, 24 cases)**		**Women (410 participants, 35 cases)**		***p*-value for interaction**
Models	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	
Model 1	0.38 (0.24-0.57)	<.001	0.66 (0.32-1.37)	.26	0.29 (0.17-0.49)	<.001	.08
Model 2	0.49 (0.31-0.80)	.004	1.04 (0.45-2.42)	.92	0.37 (0.21-0.67)	.001	.04
Model 3	0.54 (0.31-0.95)	.03	0.57 (0.22-1.46)	.24	0.56 (0.28-1.13)	.10	N/A
Model 4	0.53 (0.29-0.97)	.04	1.07 (0.43-2.67)	.89	0.41 (0.20-0.81)	.01	.06

CI, confidence interval; HR, hazard ratio; HRs are reported per standard deviation increase

Model 1: Adjusted for age and sex (not adjusted for sex in the sex-specific analysis)

Model 2: Model 1 plus high-density lipoprotein cholesterol, systolic blood pressure, smoking status, physical activity, family history of diabetes and fasting plasma glucose

Model 3: Sex, smoking, parental history of diabetes, hypertension and waist circumference (adjusted for smoking, hypertension and waist circumference in men and parental history of diabetes, hypertension and waist circumference in women)

Model 4: Age, sex, waist circumference, smoking, parental diabetes, hypertension and glucose (not adjusted for sex in the sex-specific analyses)

TABLE 3 Risk discrimination and reclassification upon addition of normalized handgrip strength to the DESIR T2D risk prediction model containing conventional risk factors

Discrimination	**Overall**	**Men**	**Women**
C-index (95% CI): conventional risk factors	0.6596 (0.5904 to 0.7288)	0.5508 (0.4303 to 0.6713)	0.7441 (0.6697 to 0.8185)
C-index (95% CI): conventional risk factors plus HGS	0.6979 (0.6261 to 0.7698)	0.6326 (0.5284 to 0.7368)	0.7588 (0.6804 to 0.8371)
C-index change (95% CI)	0.0383 (-0.0047 to 0.0814)	0.08181 (-0.0429 to 0.2065)	0.0147 (-0.0167 to 0.0460)
p-value	.08	.20	.36
p-value for difference in -2 log likelihood	.01	.25	.03
Reclassification			
Continuous Net reclassification index (95% CI)	33.26% (-18.09 to 84.60)	55.20% (-44.08 to 154.49)	15.09% (-49.11 to 79.29)
p-value	.20	.28	.65
Integrated discrimination index (95% CI)	0.0122 (0.0002 to 0.0242)	0.0075 (-0.008 to 0.0178)	0.0160 (-0.0001 to 0.0321)
p-value	.05	.16	.05

The model with conventional risk factors included sex, smoking, parental history of diabetes, hypertension and waist circumference (smoking, hypertension and waist circumference for men and parental history of diabetes, hypertension and waist circumference for women)

DESIR, Data from the Epidemiological Study on the Insulin Resistance Syndrome; HGS, handgrip strength; T2D, type 2 diabetes

TABLE 4 Risk discrimination and reclassification upon addition of normalized handgrip strength to the KORA S4/F4 T2D risk prediction model containing conventional risk factors

Discrimination	**Overall**	**Men**	**Women**
C-index (95% CI): conventional risk factors	0.8052 (0.7462 to 0.8642)	0.7255 (0.6146 to 0.8365)	0.8634 (0.8060 to 0.9207)
C-index (95% CI): conventional risk factors plus HGS	0.8234 (0.7646 to 0.8821)	0.7780 (0.6791 to 0.8770)	0.8758 (0.8206 to 0.9310)
C-index change (95% CI)	0.0182 (-0.0079 to 0.0443)	0.0525 (-0.0059 to 0.1108)	0.0124 (-0.0046 to 0.0295)
p-value	.17	.08	.15
p-value for difference in -2 log likelihood	.01	.33	.04
Reclassification			
Continuous Net reclassification index (95% CI)	58.44% (35.16 to 81.72)	55.58% (-41.47 to 152.64)	59.90% (28.18 to 91.63)
p-value	<.001	.26	<.001
Integrated discrimination index (95% CI)	0.1965 (0.1403 to 0.2527)	0.0125 (-0.0024 to 0.0275)	0.3236 (0.2350 to 0.4122)
p-value	<0.001	.10	<.001

The model with conventional risk factors included age, sex, waist circumference, parental history of diabetes, smoking and hypertension (sex was not included in the separate models for men and women)

KORA Cooperative Health Research in the Region of Augsburg; HGS, handgrip strength; T2D, type 2 diabetes

Supplementary Material

Supplementary Material 1	STROBE 2007 Statement—Checklist of items that should be included in reports of cohort studies
Supplementary Material 2	Participant flow
Supplementary Material 3	Baseline participant characteristics, overall and by sex
Supplementary Material 4	Imputed results for the overall and sex-specific association of normalized handgrip strength with type 2 diabetes

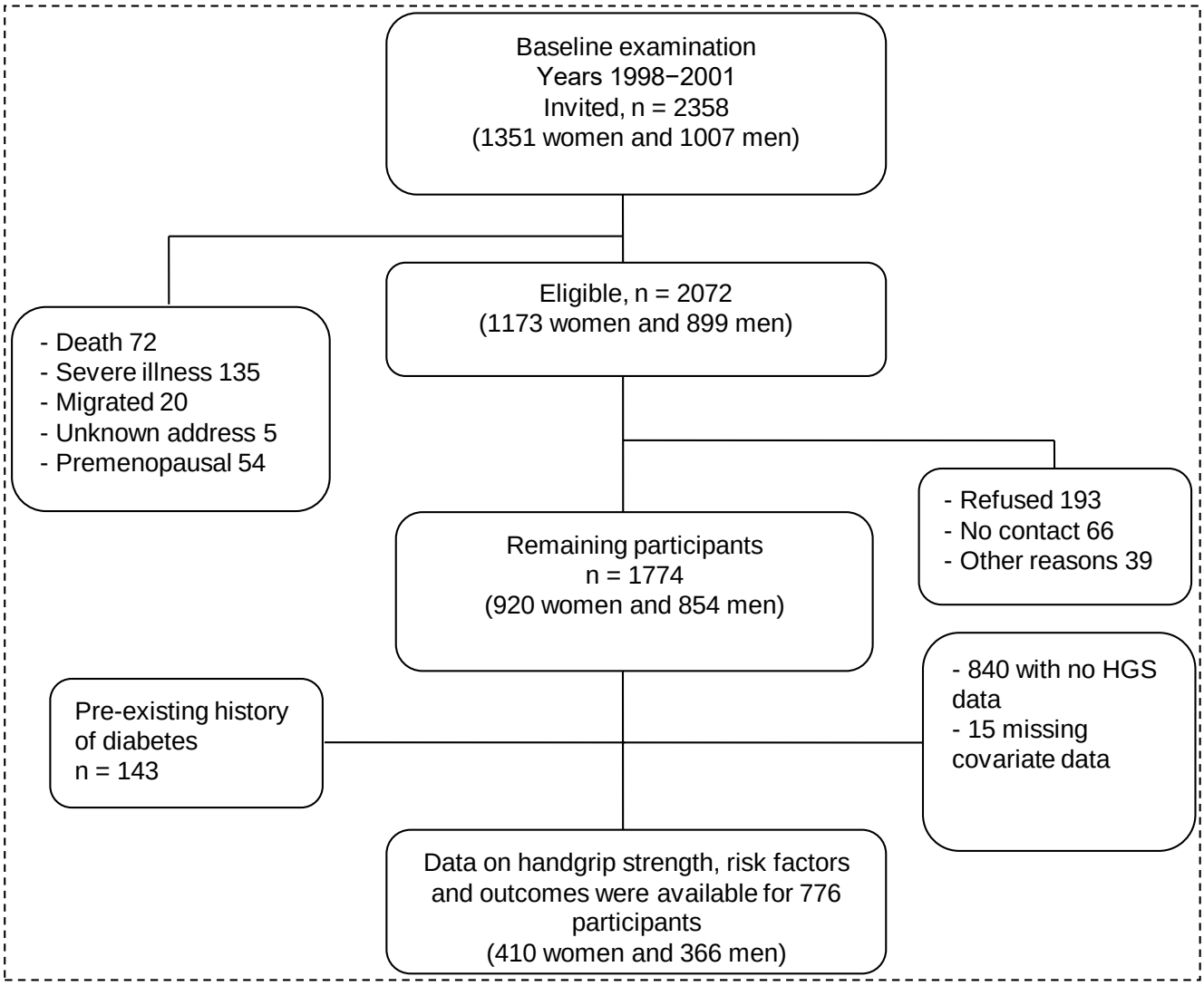
Supplementary Material 1: STROBE 2007 Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Study design and population
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Study design and population
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Study design and population
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Study design and population
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Assessment of HGS and relevant risk markers; Ascertainment of incident T2D
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Assessment of HGS and relevant risk markers

Bias	9	Describe any efforts to address potential sources of bias	Statistical analysis
Study size	10	Explain how the study size was arrived at	Statistical analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	Statistical analysis
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Statistical analysis
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplementary Material 2
		(b) Give reasons for non-participation at each stage	Supplementary Material 2
		(c) Consider use of a flow diagram	Supplementary Material 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	Results
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results; Tables 2-4

		(*b*) Report category boundaries when continuous variables were categorized	Results; Tables 2-4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary Material 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgement

Supplementary Material 2: Participant flow



HGS, handgrip strength

Supplementary Material 3: Baseline participant characteristics, overall and by sex

	Overall (N=776) Mean (SD), median (IQR) or n (%)	**Women (N=410) Mean (SD), median (IQR) or n (%)**	**Men (N=366) Mean (SD), median (IQR) or n (%)**
Normalized handgrip strength (kPa/kg$^{2/3}$)	0.49 (0.23)	0.54 (0.28)	0.42 (0.14)
Questionnaire/Prevalent conditions			
Age at survey (years)	69 (3)	69 (3)	68 (3)
Family history of diabetes	258 (33.3)	139 (33.9)	119 (32.5)
Current smokers	74 (9.5)	18 (4.4)	56 (15.3)
History of hypertension	347 (44.7)	201 (49.0)	146 (39.9)
Physical measurements			
Weight (kg)	75.2 (12.9)	71.2 (12.8)	79.7 (11.5)
Height (cm)	164 (9)	158 (5)	171 (6)
BMI (kg/m^2)	27.9 (4.3)	28.6 (4.9)	27.1 (3.4)
Waist circumference (cm)	92.4 (11.7)	88.5 (11.6)	96.8 (10.0)
SBP (mmHg)	139 (18)	140 (18)	137 (18)
DBP (mmHg)	80 (9)	79 (9)	81 (9)
Energy expenditure of total LTPA (kcal/day)	386 (232-680)	376 (230-630)	393 (242-693)
Blood-based markers			
Total cholesterol (mmol/l)	5.48 (0.93)	5.72 (0.94)	5.21 (0.85)
HDL-C (mmol/l)	1.25 (0.31)	1.35 (0.32)	1.14 (0.26)
FPG (mmol/l)	4.90 (0.52)	4.83 (0.48)	4.98 (0.55)

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LTPA, leisure-time physical activity; SD, standard deviation; SBP, systolic blood pressure; T2D, type 2 diabetes

Supplementary Material 4: Imputed results for the overall and sex-specific association of normalized handgrip strength with type 2 diabetes

	Overall (1,631 participants, 114 cases)		**Men (774 participants, 56 cases)**		**Women (857 participants, 58 cases)**	
Models	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Model 1	0.47 (0.35-0.62)	<.001	0.66 (0.42-1.05)	.08	0.37 (0.26-0.53)	<.001
Model 2	0.58 (0.42-0.82)	.002	0.86 (0.49-1.51)	.60	0.46 (0.30-0.71)	.001
Model 3	0.67 (0.45-1.00)	.05	0.77 (0.43-1.38)	.36	0.64 (0.39-1.05)	.08
Model 4	0.65 (0.41-1.05)	.08	0.78 (0.40-1.52)	.45	0.59 (0.32-1.10)	.09

CI, confidence interval; HR, hazard ratio; HRs are reported per standard deviation increase

Model 1: Adjusted for age and sex (not adjusted for sex in the sex-specific analysis)

Model 2: Model 1 plus high-density lipoprotein cholesterol, systolic blood pressure, smoking status, physical activity, family history of diabetes and fasting plasma glucose

Model 3: Sex, smoking, parental history of diabetes, hypertension and waist circumference (adjusted for smoking, hypertension and waist circumference in men and parental history of diabetes, hypertension and waist circumference in women)

Model 4: age, sex, waist circumference, smoking, parental diabetes, hypertension and glucose (not adjusted for sex in the sex-specific analyses)